REMARKS

At the outset, Applicants' representative wishes to thank Examiner Mitchell for the helpful and courteous discussion held with her on December 4, 2003, during which the prosecution of the above-identified application was materially advanced. The following remarks will expand and summarize the issues discussed.

The present claims relate to pressurized metered dose inhalers ("MDIs"), which contain a solution comprising an active ingredient, a hydrofluorocarbon propellant, and a cosolvent, wherein said inhaler has an internal surface and all or part of said internal surface is a material selected from the group consisting of stainless steel and anodized aluminum.

The inventors have surprisingly found that the presently claimed MDIs unexpectedly reduce the chemical degradation of the active ingredient contained in the MDI. The cited references contains no disclosure or suggestion of such a MDI. Moreover, these references contain no teaching which would suggest the improved chemical stability of the active ingredient contained in the presently claimed MDI. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 11-44 under 35 U.S.C. § 103(a) in view of U.S. Patent No. 5,676,930 (Jager et al) in view of U.S. Patent No. 6,143,277 (Ashurst et al) is respectfully traversed. Specifically, as explained in more detail below, one of skill in the art would not have been motivated to use the container of Ashurst et al for the solutions of Jager et al. Moreover, even the combined teachings of Jager et al and Ashurst et al do not suggest the advantages afforded by the presently claimed MDI.

Jager et al discloses certain stabilized medicinal aerosol solution formulations. However, as conceded on page 3 of the Office Action, this reference neither discloses nor suggests any ("MDIs"), in which all or part of said internal surface is a material selected from the group consisting of stainless steel and anodized aluminum.

Ashurst et al discloses certain MDIs in which all or part of the internal surface is coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising salmeterol.

However, as clearly stated in column 1, lines 19-26 and lines 29-33, the drug, salmeterol, is present in the inhalation formulation as a finely divided powder ***suspended*** in a liquefied propellant (*see also*, the Examples at cols. 7 to 10). Ashurst et al discloses that the technical problem in this kind of suspension formulation is that:

> Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI.
>
> *See*, col. 1, lines 51-54.

The solution to this problem proposed in Ashurst et al is to use a MDI in which the interior surface is coated with a fluorocarbon polymer (*see*, col. 1, lines 59-63).

Thus, Ashurst et al is only concerned with a problem which is specific to suspensions and does not disclose any MDI which contain a solution of an active agent.

In sharp contrast, the present claims explicitly recite that the MDI contains "a ***solution*** comprising an active ingredient." As explained above, the inventors have discovered that the presently claimed MDI unexpectedly afford a dramatic improvement in the chemical stability of the active ingredient in the solution contained in the MDI.

As explained in the previously-filed response, the distinction between Ashurst et al and the presently claimed MDI is discussed in the present specification. Specifically, Ashurst et al is related to WO 96/32150, which is discussed on page 3 of the present specification:

> WO 96/32099, WO 96/32150, WO 96/32151 and WO 96/32345 disclose metered dose inhalers for the administration of different active ingredients ***in suspension*** in the propellant, wherein the internal surfaces of the inhaler are partially or completely coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers.
>
> Said applications do not however address the technical problem of ***the chemical stability of the active ingredient but they rather concern a different problem, namely that of the adhesion of micronized particles of the suspended active ingredient to the internal surfaces of the inhaler, such as the can walls, valves and sealings***.
>
> page 3, lines 15-28, emphasis added.

In sharp contrast, the problem solved by the present invention is quite distinct from that of Ashurst et al. As explained on page 3, lines 4-6, of the present specification, "the widespread use of [HFA solution] formulations is limited by their chemical instability, causing the formation of degradation products." In other words, the present invention relates

to a pressurized metered dose inhaler which contains a ***solution*** comprising an active ingredient, wherein said inhaler has an internal surface and all or part of said internal surface is a material selected from the group consisting of stainless steel and anodized aluminum. As explained on pages 4-6 of the present specification, the inventors have found that:

> the chemical stability problems of active ingredients in solution in HFA propellants can be eliminated by storing and delivering said composition employing metered-dose inhalers having part or all of their internal metallic surfaces consisting of stainless steel, anodized aluminum or lined with an inert organic coating.
>
> The preferred material for the aerosol cans is anodized aluminum.
>
> *See*, page 4, line 26, to page 5, line 5.
>
> * * *
>
> The inhalers according to the invention effectively prevent the chemical degradation of the active ingredient.
>
> See, page 5, lines 26-28.
>
> * * *
>
> Active ingredients which may be used in the aerosol compositions to be dispensed with the inhalers of the invention are any ingredient which can be administered by inhalation and which meets ***problems of chemical stability in solution in HFA propellants*** giving rise to a decomposition when stored in conventional materials cans and in particular in aluminum cans.
>
> See, page 6, line 28, to page 7, line 7.

There is no disclosure of the problem of chemical stability Ashurst et al. At most, one would look to the disclosure of Ashurst et al to address the specific disclosed problem with ***suspensions***. Since the present claims are directed toward MDI which contain a ***solution*** of the active ingredient, one of skill in the art would not look to Ashurst et al to address the problem of chemical stability encountered with such solutions.

A. One Of Skill In The Art Would Not Have Been Motivated To Use The Container Of Ashurst et al For The Solutions Of Jager et al.

As explained above, at most Ashurst et al suggests the use of a specific type of container to address certain problems associated with ***suspensions***. There is no teaching in Ashurst et al which would suggest any benefit to using an MDI, which has an internal surface made of a material selected from the group consisting of stainless steel and anodized aluminum as a container for a ***solution*** comprising an active ingredient, a hydrofluorocarbon propellant, and a cosolvent.

Since Ashurst et al is only concerned with the problems encountered with ***suspensions*** and provides no suggestion of any improvement to be obtained by using an MDI, which has an internal surface made of a material selected from the group consisting of stainless steel and anodized aluminum as a container for a ***solutions***, one of skill in the art would not have been motivated to use an MDI, which has an internal surface made of a material selected from the group consisting of stainless steel and anodized aluminum as a container for a ***solution***. Accordingly, one of skill in the art would not have been motivated

to use the container of Ashurst et al for the solutions of Jager et al. In other words, the skilled artisan would not combine the teachings of these references.

B. Even The Combined Disclosures Of Jager et al And Ashurst et al Do Not Suggest The Advantages Afforded By The Presently Claimed MDI.

Even if the teachings of Jager et al and Ashurst et al are combined there is still no suggestion of the improvements afforded by the presently claimed MDI. As explained above, the present inventors have found that the presently claimed inhalers effectively ***prevent the chemical degradation of the active ingredient***. There is no teaching in either of the cited references which would suggest this result. As noted above, Ashurst et al is only concerned with the adhesion of the micronized particles of the suspended active ingredient to the internal surfaces of the inhaler. As also noted above, Jager et al does not suggest any improvement to be obtained by using an MDI which has an internal surface made of a material selected from the group consisting of stainless steel and anodized aluminum.

Thus, even the combined teachings of the cited references do not suggest that the use of an MDI which has an internal surface made of a material selected from the group consisting of stainless steel and anodized aluminum would result in improvement of the chemical stability of the active ingredient.

For all of these reasons, the rejection should be withdrawn.

C. The Data In Table 3.

As explained in the previously filed response, there are some errors in Table 3 on page 19, of the specification as filed. Specifically, the numbers given for the amounts of citric acid in the first two rows of data are incorrect. As also noted in the previously filed response, the data in the first two rows of Table 3, on page 19 of the specification, do not represent the best mode of carrying out the invention as contemplated by the inventors at the time the application was filed.

On page 2, of the Office Action, the Examiner states that she is uncertain as to what the inventors considered as the best mode and that it is unclear that the Applicant "actually had possession of the best mode" at the time the application was filed. However, Applicants note that there is no requirement that there be a best mode. Instead, the Applicants are only required to disclose the best mode, if one existed. *Eli Lilly & Co. v. Barr Laboratories, Inc.*, 251 F.3d 955, 58 USPQ2d 1869 (Fed. Cir. 2001), a copy of which is attached.

In the specific case of Table 3, Applicants have already stated on the record that the data in the first two rows of Table 3, on page 19 of the specification, do not represent the best mode of carrying out the invention as contemplated by the inventors at the time the application was filed. Applicants also repeat their offer to amend Table 3 to either cancel or correct the erroneous data.

Lastly, Applicants wish to thank Examiner Mitchell for returning an initialed copy of the Form PTO 1449 filed with the Information Disclosure Statement ("IDS") filed on March 31, 2003. However, Applicants note that the Examiner did not place her initials next to Reference AW (R. O. Williams et al) on the copy of page 1 of the Form PTO 1449. Although it is assumed that this was merely an oversight, another copy of R. O. Williams et al is being submitted with the IDS being filed herewith.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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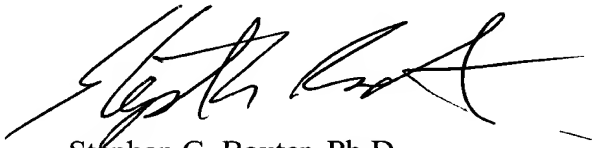

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